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Diet and the risk of *in situ* cervical cancer among white women in the United States

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A case-control study of women with incident *in situ* and invasive cervical cancer was conducted during 1982-83 in five US areas reporting to the Comprehensive Cancer Patient Data System: Birmingham, AL; Chicago, IL; Denver, CO; Miami, FL; and Philadelphia, PA. Controls were selected by random-digit dialing and matched to invasive cases on age, race, and telephone exchange. Of the white non-Hispanic *in situ* cases and controls identified, 229 (78 percent) and 502 (74 percent) were successfully interviewed. Diet was assessed by asking about the usual adult frequency of consumption of 75 food items and the use of vitamin supplements. Included were the major sources of the four micronutrients postulated to reduce the risk of cervical cancer: carotenoids, vitamin A, vitamin C, and folate. Weak inverse associations between risk of *in situ* disease and intake of carotenoids, vitamin C, folate, fruit, and vegetables/fruits were noted but, with further analysis, these seemed attributable to residual confounding by the multiple lifestyle-related risk factors for this disease and possibly to selection bias. Vitamin A and vegetable intake were unrelated to risk. Dark yellow-orange vegetable consumption and duration of multivitamin use were each strongly related to reduced risk of *in situ* disease (P for trend = 0.02 and 0.002, respectively) and need to be evaluated in other studies. The absence of persuasive protective effects for the four micronutrients and the similar findings from our analysis of invasive cervical cancer do not concur with other epidemiologic studies and suggest that the role of diet and nutrition in the etiology of cervical cancer is not yet resolved.

Key words: Beta-carotene, carotenoids, cervical neoplasms, diet, folate, nutrient status, vitamin A, vitamin C, vitamin supplements, USA.

Introduction

In a large case-control study of incident invasive and *in situ* cervical cancer with community controls, conducted in five areas of the United States, we found no associations between risk of *invasive* cervical cancer and intake of carotenoids, vitamin A, vitamin C, folate, or the related food groups.[1] These negative findings did not

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concur with the published literature since a number of epidemiologic studies have suggested that these micronutrients might reduce the risk of cervical cancer.[2-19] However, the majority of the studies demonstrating relationships were of cervical dysplasia and *in situ* cervical cancer whereas we had focused our initial analysis on invasive disease. Moreover, in a case-control study conducted in England, reduced risk with high serum beta-carotene levels had been restricted to women with preinvasive cervical cancer and not observed among those with invasive disease.[13] Only one other case-control study of diet and cervical neoplasia[18] had used community controls, as we did, but its results could not be compared directly with ours for invasive disease since that study was of *in situ* cervical cancer. Thus, we wanted to determine whether our surprising findings—suggesting no protective role for micronutrients in the development of invasive cervical cancer—extended to *in situ* cervical cancer. An analysis of the other risk factors for *in situ* cervical cancer that were identified in our study has been published recently.[20]

Materials and methods

A case-control study of women with invasive and *in situ* cervical cancer was carried out in five US metropolitan areas reporting to the Comprehensive Cancer Patient Data System: Birmingham, AL; Chicago, IL; Denver, CO; Miami, FL; and Philadelphia, PA. Eligible *in situ* cases were residents of these areas, aged 20 – 74 years, who were newly diagnosed with histologically confirmed *in situ* cancer of the uterine cervix at one of 24 participating hospitals during the period 15 April 1982 through 31 August 1983 (Birmingham, Miami, and Philadelphia) or 15 April 1982 through 31 December 1983 (Chicago and Denver). Controls from the same communities were selected by random-digit dialing techniques.[21,22] Up to two controls were individually matched to each eligible invasive case on age (± five years), race (white, Hispanic, black), and neighborhood (first three digits of telephone exchange).[23] Cases were matched to invasive controls, since elucidating the etiology of invasive cervical cancer was the primary focus of this study. Approximately 26 percent of the selected controls had had a hysterectomy and were replaced with others from the control pool. Cases and controls with a history of cancer of a genital organ were excluded.

Denver was the only study center to ascertain cases from all hospitals within a defined geographic area, including community hospitals. Birmingham, Chicago, Miami, and Philadelphia identified cases primarily through large urban teaching hospitals. Also in Denver, eligible cases were sampled such that one in six *in situ* cases aged less than 30 years, one in three aged 30 – 39, and all aged 40 or more were randomly selected, to reduce the age discrepancy anticipated between *in situ* cases and controls matched on age to invasive cases.

Similar to our analysis of invasive disease, the present analysis is restricted to white non-Hispanic females. The small numbers of black and Hispanic study participants with *in situ* disease, 32 and 22, respectively, precluded analysis of these subgroups. Of the white non-Hispanic *in situ* cases and controls identified for the study, interviews were successfully completed for 229 (78 percent) and 502 (74 percent), respectively. Subject refusal (10 percent of the cases and 21 percent of the controls) was the major reason for nonparticipation. Other reasons included: subject moved or not traceable (four percent, three percent); illness or death (one percent, two percent); and other problems (0.3 percent, one percent). For seven percent of the cases, it was not possible to obtain the physician's consent to perform the interview.

The questionnaire was administered to the subject in her home by a trained interviewer and lasted, on the average, 76 minutes. It elicited detailed information on demographic characteristics, sexual behavior, reproductive and menstrual history, contraceptive and female hormone use, personal and familial medical history, smoking, and diet. Diet was assessed by asking about the "usual adult frequency of consumption, ignoring any recent changes," of 75 food items, listed in our earlier paper.[1] Included were the major sources of carotenoids, vitamin A, vitamin C, and folate in the US diet. For any vitamin supplements taken on a regular basis more than one year before the interview, intake was assessed by obtaining the usual frequency and duration of use during the last 20 years.

Estimates of both food group and nutrient intake were developed. Food group intake was calculated as the sum of the frequencies of consumption of the food items comprising the food group. Nutrient intake was calculated as the weighted sum of the frequencies of consumption of the food items containing the nutrient; weights used were the nutrient contents of typical servings of the food items. The portion size and method of preparation (fresh, frozen, or canned, etc.) of a typical serving were based on the descriptive dietary information collected for women aged 19 – 74 in the second National Health and Nutrition Examination Survey (NHANES II) during 1976 – 80.[24] Food composition data were, in general, those utilized in NHANES II, which updated the values reported in the 1963 USDA Composition of Foods.[25] However, vitamin A and carotenoid content were calculated according to the current convention that dietary beta-carotene has one-sixth the vitamin A activity of an equivalent weight of

dietary retinol.[26] Folate content was not available in the NHANES II database and was obtained from the 1978 – 88 USDA Composition of Foods,[27] recent laboratory research,[28] and proprietary sources.[28] Vitamin supplements were not included in the nutrient indices and were evaluated separately. A more detailed description of the dietary interview and the formation of the nutrient indices is presented elsewhere.[1]

Each measure of food group or nutrient intake was stratified into quartiles according to the freqency distribution among the controls in the study population. All races were combined in the frequency distribution to permit race-specific risks for dietary factors to be compared.

The one case and four controls (0.7 percent of all white subjects) who could not give frequencies of consumption for six or more of the 75 food items were eliminated from the dietary analysis. For the 228 cases and 498 controls remaining, 99.8 percent of the food items had elicited frequencies. Appropriate medians were substituted for the missing values.

The relative risk (RR), as estimated by the odds ratio, was the measure of association used to evaluate the effect of diet on cervical cancer risk. Unconditional logistic regression was performed to obtain maximum likelihood estimates of the odds ratios and 95 percent confidence intervals (CI), while adjusting for potential confounders.[29] Tests for trend were obtained by assigning the median value (for micronutrients or food groups) or mean value (for supplemental vitamins) within each categorical level of the dietary exposure to the level and entering them as a continuous variable into the logistic model. Potential confounding variables examined were: number of sexual partners; age at first intercourse; years of oral contraceptive use; years since last Papanicolau (Pap) smear screening; history of nonspecific gynecologic infection; years of cigarette smoking; usual number of cigarettes per day; years since quitting smoking; education; family income; age at diagnosis; and study center. Detailed logistic models were run in all analyses, with the number of confounding variables and/or the number of strata of each confounder were gradually reduced, in order to approach the simplest model with adequate control of confounding. In general, a potential confounder was retained when it changed an adjusted RR by 0.1 or more. The RRs and confidence limits from the simpler models are presented in the text and tables.

The controls selected for the study were matched to the invasive cervical cancer cases on neighborhood, to adjust for referral patterns to the participating hospitals. However, referral patterns were expected to be different for invasive and *in situ* disease since invasive cervical cancer requires additional treatment beyond surgery and referral to an oncology specialist while surgery for *in situ* disease can be handled on an outpatient basis or in a community hospital. A neighborhood variable was created, based on (i) the median income,[30] and (ii) the general geographic location of the zip code where the subject lived. This neighborhood variable was substituted for study center in the fully adjusted models shown in Tables 1, 2, and 4, but did not alter the RRs.

Effect modification was evaluated by deriving and comparing the adjusted RRs for each subgroup of the study subjects being considered.

Results

The white women with *in situ* cervical cancer participating in this study had a median age of 36 years and a median education of 13.0 years. Because controls had been matched to the eligible invasive cases, the comparable values for the controls were 41 years and 12.0 years, respectively. The majority of the 228 *in situ* cases, 64 percent, lived in the Denver area since it was the only study center to ascertain cases from all hospitals within a defined geographic area (community hospitals as well as urban teaching hospitals). Denver also provided the largest number, 27 percent, of the 498 controls. Chicago, Philadelphia, Birmingham, and Miami provided 24, eight, two, and one percent of the participating *in situ* cases and 22, 23, 18, and 10 percent of the participating controls. Because of these discrepancies, age, education, and study center were retained in all final models.

Based on hospital pathology records, squamous-cell cervical carcinoma *in situ* was diagnosed in 91 cases, and cervical carcinoma *in situ* NOS in 137 cases; the one case of cervical adenocarcinoma *in situ* was excluded.

Crude and adjusted RRs of *in situ* cervical cancer by decreasing intake of carotenoids, vitamin A, vitamin C, and folate are presented in Table 1. When the fully adjusted RRs are examined, weak inverse associations are seen for carotenoids, vitamin C, and folate. The highest risk among consumers in the lowest quartile of intake, a RR of 1.5, was noted for vitamin C; however, RRs by quartile of intake showed a clear trend only for folate. None of the tests for trend was statistically significant. Also, none of the CIs for the lowest quartiles of intake excluded 1.0: carotenoids, 0.7 – 2.7; vitamin A, 0.6 – 2.2; vitamin C, 0.8 – 3.2; folate, 0.7 – 2.7.

Table 1 demonstrates that there was extensive confounding of the crude associations with carotenoid, vitamin C, and folate intake. Age, study center, number of sexual partners, and duration of cigarette smoking were the major confounders although all the variables included in the final model seemed necessary for adequate control. After age and study center were added to the crude models to adjust for the major differences between cases and controls resulting from study design, significant or marginally significant trends in risk were still seen for

Table 1. Crude and adjusted relative risks (RR) of *in situ* cervical cancer by nutrient intake in white US women

Nutrient	Level of consumption				*P* for trend
	Highest quartile	Quartile 3	Quartile 2	Lowest quartile	
Carotenoids					
Crude RR	1.0	1.04	1.64	2.41	<0.0001
RR adjusted for study design[a]	1.0	0.77	1.16	1.76	0.01
Fully adjusted RR[b]	1.0	0.85	0.97	1.37	0.25
Cases, controls	(27,92)	(41,135)	(68,141)	(92,130)	
RE[c]/day	≥682	468 - 681	321 - 467	≤320	
Vitamin A					
Crude RR	1.0	0.74	0.97	1.42	0.07
RR adjusted for study design[a]	1.0	0.64	0.71	1.10	0.60
Fully adjusted RR[b]	1.0	0.56	0.73	1.13	0.49
Cases, controls	(32,73)	(45,138)	(60,141)	(91,146)	
RE/day	≥1742	1095 - 1741	732 - 1094	≤731	
Vitamin C					
Crude RR	1.0	2.23	2.59	3.09	0.0001
RR adjusted for study design[a]	1.0	1.65	1.84	2.11	0.02
Fully adjusted RR[b]	1.0	1.52	1.51	1.54	0.34
Cases, controls	(18,92)	(54,124)	(75,148)	(81,134)	
Mg/day	≥212	146 - 211	94 - 145	≤93	
Folate					
Crude RR	1.0	1.71	2.00	2.52	0.0005
RR adjusted for study design[a]	1.0	1.35	1.50	1.71	0.08
Fully adjusted RR[b]	1.0	1.08	1.27	1.37	0.29
Cases, controls	(21,87)	(52,126)	(71,147)	(84,138)	
μg/day	≥303	230 - 302	172 - 229	≤171	

[a]Adjusted for age at diagnosis and study center.
[b]Adjusted for number of sexual partners, duration of cigarette use, duration of oral contraceptive use, history of nonspecific genital infection, years since last Pap smear, years of education, age at diagnosis, and study center.
[c]Retinol equivalents.

carotenoid, viamin C, and folate intake but were eliminated by addition to the models of risk factors for cervical cancer. Addition of education as the last variable to the models to assess uncontrolled confounding by aspects of lifestyle not fully evaluated in the interview, slightly increased the risks associated with low micronutrient intake.

Fully adjusted RRs of *in situ* cervical cancer were recalculated for each micronutrient by decile of intake. Trends in risk with decreasing intake were not more pronounced than trends by quartile of intake. In fact, the RRs for women in the lowest decile of intake of carotenoids or folate, compared to women in the highest decile, did not exceed 1.0; and the RR for women in the lowest decile of intake of vitamin C, although elevated compared to that for the highest decile, was similar to the RRs seen at all intermediate levels of intake.

Table 2 presents the crude and adjusted RRs of *in situ* cervical cancer by intake of basic food groups—fruits, vegetables, legumes, complex carbohydrates, dairy products, and meat and fish. Also included are two vegetable subgroups postulated to reduce cancer risk: dark green and dark yellow-orange vegetables;[31] and two meat/fish subgroups that might indicate the affluence of the diet. For dark yellow-orange vegetables, the fully adjusted RRs steadily increased as intake decreased, and the trend was statistically significant. The CI for the risk associated with the lowest quartile of dark yellow-orange vegetable consumption marginally excluded 1.0: 1.01 - 3.5. For vegetables/fruits and for fruits, the fully adjusted risk was elevated at low intake, but the trends were not significant. Significant trends in risk with decreasing intake were seen for vegetables/fruits, fruits, and vegetables after adjustment for age and study center, but disappeared when other cervical cancer risk factors were entered into the model. Other food groups were not associated with risk of *in situ* cervical cancer.

Table 2. Crude and adjusted relative risks (RR) of *in situ* cervical cancer by food group intake in white US women

Food group	Level of consumption				*P* for trend
	Highest quartile	Quartile 3	Quartile 2	Lowest quartile	
Vegetables and fruit					
Crude RR	1.0	1.90	1.93	2.74	0.0001
RR adjusted for study design[a]	1.0	1.55	1.59	1.99	0.02
Fully adjusted RR[b]	1.0	1.44	1.49	1.36	0.43
Cases, controls	(25,105)	(62,137)	(62,135)	(79,121)	
Servings/week	≥44	31 – 43	22 – 30	≤21	
Fruits					
Crude RR	1.0	1.58	1.97	2.85	<0.0001
RR adjusted for study design[a]	1.0	1.09	1.42	2.27	0.001
Fully adjusted RR[b]	1.0	1.02	1.07	1.64	0.09
Cases, controls	(25,104)	(48,126)	(64,135)	(91,133)	
Servings/week	≥19	13 – 18	7.4 – 12	≤7.3	
Vegetables					
Crude RR	1.0	1.22	1.53	2.01	0.002
RR adjusted for study design[a]	1.0	0.95	1.38	1.56	0.04
Fully adjusted RR[b]	1.0	0.89	1.32	1.08	0.48
Cases, controls	(38,118)	(54,138)	(66,134)	(70,108)	
Servings/week	≥26	18 – 25	12 – 17	≤11	
Dark green vegetables					
Crude RR	1.0	1.43	1.37	1.63	0.04
RR adjusted for study design[a]	1.0	1.27	1.20	1.22	0.45
Fully adjusted RR[b]	1.0	1.17	1.38	0.96	0.80
Cases, controls	(46,135)	(62,127)	(59,126)	(61,110)	
Servings/week	≥6.3	4.1 – 6.2	2.5 – 4.0	≤2.4	
Dark yellow-orange vegetables					
Crude RR	1.0	0.94	1.59	1.79	0.005
RR adjusted for study design[a]	1.0	0.99	1.81	2.01	0.003
Fully adjusted RR[b]	1.0	1.25	1.81	1.88	0.02
Cases, controls	(39,113)	(45,138)	(71,129)	(73,118)	
Servings/week	≥2.5	1.3 – 2.4	0.55 – 1.2	≤0.54	
Legumes					
Crude RR	1.0	1.02	1.19	1.69	0.03
RR adjusted for study design[a]	1.0	0.78	0.97	1.09	0.66
Fully adjusted RR[b]	1.0	0.95	1.06	0.98	0.96
Cases, controls	(43,115)	(49,128)	(59,133)	(77,122)	
Servings/week	≥7.4	4.7 – 7.3	2.9 – 4.6	≤2.8	
Complex carbohydrates					
Crude RR	1.0	1.11	1.44	1.55	0.04
RR adjusted for study design[a]	1.0	0.90	1.08	0.99	0.87
Fully adjusted RR[b]	1.0	0.86	0.85	0.83	0.58
Cases, controls	(38,107)	(51,129)	(69,135)	(70,127)	
Servings/week	≥21	15 – 20	11 – 14	≤10	
Dairy products					
Crude RR	1.0	1.08	0.89	0.66	0.12
RR adjusted for study design[a]	1.0	1.10	1.13	0.83	0.75
Fully adjusted RR[b]	1.0	1.27	1.19	0.68	0.50
Cases, controls	(65,131)	(71,133)	(59,133)	(33,101)	
Servings/week	≥14	8.5 – 13	4.5 – 8.4	≤4.4	

Continued . . .

Table 2. *Continued*

Food group	Level of consumption				*P* for trend
	Highest quartile	Quartile 3	Quartile 2	Lowest quartile	
Meat and fish					
Crude RR	1.0	0.78	0.88	1.13	0.57
RR adjusted for study design[a]	1.0	0.79	0.91	1.11	0.64
Fully adjusted RR[b]	1.0	1.04	0.91	1.26	0.56
Cases, controls	(54,111)	(51,134)	(56,131)	(67,122)	
Servings/week	≥15	12 - 14	8.8 - 11	≤8.7	
Expensive meat and fish					
Crude RR	1.0	0.79	1.16	0.91	1.00
RR adjusted for study design[a]	1.0	0.81	1.04	0.86	0.74
Fully adjusted RR[b]	1.0	0.80	1.06	0.67	0.30
Cases, controls	(53,111)	(50,132)	(65,117)	(60,138)	
Servings/week	≥8.8	6.6 - 8.7	5.1 - 6.5	≤5.0	
Inexpensive meat and fish					
Crude RR	1.0	1.45	1.00	1.47	0.35
RR adjusted for study design[a]	1.0	1.61	1.13	1.60	0.23
Fully adjusted RR[b]	1.0	1.48	1.09	1.68	0.25
Cases, controls	(43,116)	(83,154)	(47,127)	(55,101)	
Servings/week	≥6.5	4.0 - 6.4	2.3 - 3.9	≤2.2	

[a]Adjusted for age at diagnosis and study center.

[b]Adjusted for number of sexual partners, duration of cigarette use, duration of oral contraceptive use, history of nonspecific genital infection, years since last Pap smear, years of education, age at diagnosis, and study center.

When the fully adjusted RRs of *in situ* cervical cancer were recalculated for the food groups by decile of intake, there was no evidence of increasing risk with decreasing intake for vegetables/fruits or fruits. However, for dark yellow-orange vegetables, the RRs, although unstable, did seem to increase consistently as intake decreased.

Case ascertainment was population-based only in Denver, and the majority of the *in situ* cases lived in the Denver area. In addition, participating *in situ* cases and controls from Denver had the same median education, 13.0 years, although median ages differed—36 and 40 years, respectively. Thus, fully adjusted RRs of *in situ* cervical cancer by nutrient and food group intake were derived for the 147 cases and 132 controls from Denver. The RRs for vitamin C and folate were less indicative of inverse associations than the RRs presented in Table 1. For vitamin C, RRs for the highest to lowest quartiles of intake were 1.0, 1.27, 1.15, and 1.42; for folate, 1.0, 0.89, 0.69, and 1.09. Restricting the analysis to Denver subjects strengthened somewhat the weak inverse association with vegetable intake but diminished the inverse association with fruits. However, for carotenoids, clearly increased risk at the lowest quartile of intake was observed, with fully adjusted RRs by decreasing intake from 1.0, 0.86, and 1.17, to 2.00 (*P* for trend = 0.10). Among the Denver subjects, as among the whole study population, risk increased sharply with decreasing yellow-orange vegetable consumption, rising from 1.0 to 1.35, 2.31, and 2.33 (*P* for trend = 0.03).

Of all the nutrients and food groups evaluated, only the inverse association between dark yellow-orange vegetables and *in situ* cervical cancer risk was strong and showed a graded response, in all study subjects and in Denver. Although no analogous association with risk of invasive cervical cancer had initially been observed in this study,[1] such an association may have been restricted to Denver residents or to the younger ages characteristic of *in situ* disease. Further analysis indicated that risk of invasive cervical cancer was not inversely related to yellow-orange vegetable consumption in women less than 46 years of age. However, in Denver, risk of invasive disease was approximately doubled among women in the two lowest quartiles of intake.

The weak inverse associations between *in situ* cervical cancer risk and intake of carotenoids, vitamin C, folate, and vegetables/fruits are not independent of one another. As demonstrated in Table 3, these five dietary exposures were highly intercorrelated among the white women participating in this study. The pairwise correlation coefficients for carotenoid, vitamin C, and folate intake range from 0.69 to 0.76. The vegetables/fruits food group has correlation coefficients of 0.82 and 0.80 with carotenoids and vitamin C, respectively. However, the correlation of other food groups, such as meat and

Table 3. Spearman correlation coefficients for nutrient and food group intake in white US women[a]

	Car	A	C	Fol	V,f	Fruit	Vegs	Gr veg	Y-o veg	Leg	Carb	Dairy
Carotenoids	1.0											
Vitamin A	0.65	1.0										
Vitamin C	0.70	0.50	1.0									
Folate	0.69	0.63	0.76	1.0								
Vegetables and fruit	0.82	0.58	0.80	0.74	1.0							
Fruit	0.64	0.43	0.82	0.69	0.83	1.0						
Vegetables	0.75	0.57	0.58	0.59	0.87	0.47	1.0					
Dark green vegetables	0.63	0.45	0.45	0.54	0.58	0.35	0.66	1.0				
Dark yellow-orange vegs	0.63	0.46	0.37	0.35	0.53	0.32	0.57	0.35	1.0			
Legumes	0.39	0.30	0.31	0.48	0.39	0.28	0.40	0.44	0.30	1.0		
Complex carbohydrates	0.23	0.26	0.23	0.43	0.21	0.20	0.17	0.15	0.15	0.13	1.0	
Dairy products	0.26	0.36	0.25	0.37	0.22	0.22	0.18	0.17	0.17	0.21	0.22	1.0
Meat and fish	0.18	0.32	0.17	0.35	0.20	0.11	0.22	0.23	0.08	0.22	0.27	0.16

[a]Intercorrelations were examined in the 498 controls. Continuous forms of the nutrient and food group variables were utilized.

fish, dairy products, and complex carbohydrates, with these five dietary exposures was quite low. This suggests that the high correlations noted were not simply due to certain individuals eating more of most foods because of increased weight, exercise, or metabolism.

Of particular interest was the influence of folate intake on the risk of cervical cancer in long-term oral contraceptive users. Oral contraceptive use has been thought to deplete folate in the cervical epithelium,[6,32] which could possibly explain the increased risk of *in situ* and invasive cervical cancer associated with long-term oral contraceptive use in this and other studies.[20,33] Among the 78 *in situ* cases and 99 controls in this study who had taken oral contraceptives for five or more years, there was only one case, but 13 controls, in the highest quartile of folate consumption. However, when the study controls who were long-term oral contraceptive users were divided into quartiles of folate intake, risk of *in situ* cervical cancer was not consistently related to folate consumption. Fully adjusted RRs were 1.0, 0.80, 4.19, and 1.15 with high folate consumers as the referent group.

Among the controls in this study, 270 (54 percent) had used a vitamin supplement regularly for some period during the last 20 years. Twenty percent had taken a multivitamin supplement; 26 percent a multivitamin supplement and at least one other specific supplemental vitamin; and eight percent, one or more specific supplemental vitamins, but no multivitamins. Since many of the women in the study were able to provide the type and brand of multivitamin supplement generally used, estimates of duration of supplemental vitamin A, vitamin C, folate, and vitamin E intake could be derived, based on the formulation of the multivitamin supplement reported and any use of specific supplemental vitamins. No one reported the use of beta-carotene supplements, and beta-carotene was not included in multivitamin preparations at the time of this study. Respondent information on dosage of supplemental vitamins used was inadequate for the calculation of dose-years of specific micronutrients.

Multivitamin use was associated with a reduced risk of *in situ* cervical cancer; the adjusted RR for multivitamin users, relative to multivitamin nonusers, was 0.56 (0.37 – 0.85). The adjusted RRs for users of vitamin A, vitamin C, folate, and vitamin E, relative to nonusers of the corresponding vitamin, were slightly less reduced: 0.65, 0.77, 0.75, and 0.64, respectively. As shown in Table 4, risk decreased steadily with years of use, reaching 0.4 – 0.5 for 16 or more years; all the trends with duration were statistically significant. The reduction in risk with extended use (10 or more years) and the downward trend in risk with duration were most pronounced for multivitamin use. However, because

Table 4. Adjusted[a] relative risks of *in situ* cervical cancer by duration of supplemental vitamin use in white US women

Supplemental vitamin	Years of use					*P* for trend
	0	1 – 3	4 – 9	10 – 15	16 +	
Multivitamins	1.0	0.88	0.58	0.38	0.42	0.002
	(133,268)[b]	(29,55)	(35,64)	(21,63)	(10,43)	
Vitamin A	1.0	0.79	0.69	0.62	0.48	0.04
	(139,297)	(22,48)	(35,57)	(22,54)	(10,38)	
Vitamin C	1.0	1.10	0.80	0.68	0.45	0.03
	(111,252)	(30,63)	(45,65)	(29,67)	(12,44)	
Folate	1.0	1.16	0.78	0.58	0.49	0.03
	(127,287)	(29,49)	(39,60)	(23,58)	(10,39)	
Vitamin E	1.0	0.94	0.64	0.52	0.40	0.007
	(127,267)	(32,63)	(37,64)	(22,60)	(10,39)	

[a]Adjusted for number of sexual partners, duration of cigarette use, years since last Pap smear, age at diagnosis, study center, and years of education. Other cervical cancer risk factors were not confounders.
[b]In parentheses are the numbers of cases and controls.

much of the supplemental micronutrient intake was derived from multivitamin use, the exposure estimates in Table 4 are highly correlated.

At first, confounding of the RRs of *in situ* cervical cancer by supplemental vitamin use seemed limited; the crude RRs by duration of multivitamin use were 1.0, 1.06, 1.10, 0.67, and 0.47. However, both positive and negative confounding was involved, and clear patterns were not seen. In general, the number of sexual partners is associated with years of multivitamin use. Nonusers of multivitamins had the most elapsed time since the last Pap smear, although, among multivitamin users, elapsed time increased with years of use. Education seemed directly correlated with years of multivitamin use, but the relationship with smoking was ambiguous.

When analysis was restricted to the Denver subjects, the risk of *in situ* cervical cancer remained reduced among each of the five groups of supplemental vitamin users, though to a lesser extent than among the entire study population. Moreover, risk did not decrease as steadily with duration. For each of the five groups, adjusted RRs of 0.9 – 1.0, relative to nonusers, were seen among users for one to three years; the RRs then dropped to 0.5 – 0.7, depending on the supplement, among users for four or more years. As with the entire study population, the most pronounced reduction in risk was associated with multivitamin use.

In order to examine the combined effects of diet and vitamin supplements for vitamin A, vitamin C, and folate, adjusted RRs were calculated by quartile of dietary micronutrient intake among women who had taken a vitamin supplement containing the micronutrient for more than three years (extended users) and among women who had not (limited users). Among the limited users of supplemental vitamin C or folate, the increase in risk of *in situ* cervical cancer with decreasing dietary intake of the respective micronutrient was not enhanced beyond that previously noted. In addition, the reduction in risk among extended users of supplemental vitamin C or folate, relative to limited users of the micronutrient, observed among women in the lowest quartile of dietary intake of the respective micronutrient was no more pronounced than the reduction of risk among women in the highest quartiles of intake.

Finally, the independence of the inverse associations with duration of multivitamin use and dark yellow-orange vegetable consumption were investigated. These two exposures were correlated; 17 – 19 percent of the study controls who did not use multivitamins or who took them for less than 10 years were in the highest quartile of yellow-orange vegetable consumption while 30 percent and 44 percent of those who took multivitamins for 10 – 15 and 16 or more years, respectively, were in the highest quartile. Introduction of yellow-orange vegetables into the fully adjusted model for multivitamin use had no discernible effect, with the RRs for one to three, four to nine, 10 – 15. and 16 or more years of use, relative to nonuse, becoming 0.88, 0.58, 0.38, and 0.42. However, after adjusting the RRs associated with dark yellow-orange vegetable consumption for duration of multivitamin use, the elevated risk with low intake was reduced by about one-third, with the resultant RRs by decreasing quartile of intake becoming 1.0, 1.07, 1.63, and 1.57.

Discussion

In this analysis of the dietary risk factors for *in situ* cervical cancer among white US women, weak inverse associations were seen for carotenoids, vitamin C, folate, fruit, and vegetables/fruits. Fully adjusted RRs for women in the lowest quartile of intake, relative to the highest quartile, ranged from 1.4 to 1.6. However, none of the tests for trend in risk by quartile of intake was statistically significant, and none of the RRs associated with the lowest quartile of intake was significantly different from 1.0. The inverse associations were not persuasive when deciles of intake were compared and, except for carotenoids, were weakened when analysis was restricted to Denver, the only study center with a representative series of incident *in situ* cases. In addition, the inverse associations with dietary vitamin C and folate were not enhanced among the women who reported limited or no use of supplemental vitmain C and folate, respectively.

These weak inverse associations between risk of *in situ* cervical cancer and intake of carotenoids, vitamin C, folate, fruit, and vegetables/fruits may simply reflect selection bias and uncontrolled confounding by non-dietary risk factors:

(i) Referral patterns to hospitals and clinics differ for *in situ* and invasive cervical cancer. The controls used in the *in situ* analysis had been matched on age and neighborhood to the eligible invasive cases. We were able to adjust tightly for age in the *in situ* analysis but could only adjust loosely for neighborhood and still retain sufficient numbers of subjects. Other aspects of referral bias besides age and neighborhood were not deliberately controlled;

(ii) Residual uncontrolled confounding by the multiple lifestyle-related factors believed involved in the development of cervical cancer may also be a problem in this analysis. The RRs associated with the lowest quartiles of intake of carotenoids, vitamin C, folate, fruit, and vegetables/fruits ranged from 1.7 to 2.3, even after adjusting for age and study center (or neighborhood), but could

be reduced, to 1.4 – 1.6, after incorporating nondietary risk factors for cervical cancer into the models.

This indicates substantial confounding, not all of which may have been controlled. In addition, confounding by infection with high-risk types of papillomavirus, a probable cause of cervical cancer,[34] could not be evaluated.

Bias in dietary recall between cases and controls is not a likely explanation of our weak inverse associations. If carotenoids, vitamin A, vitamin C, or folate were strongly protective, then the cases would have had to recall eating *more* of the micronutrient than they actually consumed for bias to obscure the underlying association. It is generally postulated that cancer patients recall eating *less* because of loss of appetite due to disease. In addition, in our earlier analysis of invasive cervical cancer[1] we saw no clear differences in the micronutrient intake reported by women with early and advanced stage disease, which suggests that dietary recall was not biased by cancer symptoms. For both *in situ* and invasive disease, cases and controls remembered eating similar amounts of the basic food groups, such as meat and fish and dairy products. We did not attempt to estimate total caloric intake. While our dietary instrument included all major food sources of the micronutrients of interest, it did not evaluate the entire diet with similar detail.

Our cautious approach toward the weak inverse associations noted in the *in situ* analysis is partially due to our inability to detect in this study similar inverse relationships for inavasive disease.[1] There is less likelihood of selection bias and uncontrolled confounding in the analysis of invasive cervical cancer because controls were matched to invasive cases on age and telephone exchange and because participating hospitals were selected to optimize ascertainment of cases of invasive disease, but not necessarily of *in situ* disease. In addition, recall bias, imprecise measurement of diet, and differential participation did not readily explain the negative findings of the invasive analysis; a detailed discussion is presented in our earlier paper.[1] We do not feel that matching on neighborhood obscured dietary associations with invasive disease since micronutrient and vegetable and fruit intake were not likley to be sufficiently homogenous within as arbitrary and large a 'neighborhood' as a telephone exchange. Thus, the weak inverse associations between risk of *in situ* cervical cancer and intake of carotenoids, vitamin C, folate, fruit, and vegetables/fruit are not sufficiently convincing to counter the absence of findings in the analysis of invasive cancer, or to support a role for diet in the etiology of cervical cancer overall.

Neither the *in situ* nor the invasive analysis found vitamin A or vegetables to be protective. Therefore, in interpreting our overall case-control study of cervical cancer in white US women, we do not feel there is persuasive evidence for protection by increased intake of carotenoids, vitamin A, vitamin C, folate, vegetables, fruits, or vegetables/fruit for *in situ* or invasive cervical cancer. Power calculations indicate that, with a two-sided significance level of 0.05, this study of *in situ* and invasive cervical cancer, all histologies combined, would have had an 80 percent probability of detecting a relative risk of 1.73 among women in the lowest quartile of micronutrient intake, and a 95 percent probability of detecting a relative risk of 2.0.

Two positive findings did emerge from this study of *in situ* cervical cancer. The first was a striking reduction in risk with supplemental vitamin use. The reduction in risk of *in situ* cervical cancer became apparent after four years of supplemental vitamin use and reached RRs of 0.4 – 0.5, relative to nonusers, after 15 years of use. A reduction in risk of invasive cervical cancer became apparent only after 10 years of supplemental vitamin use and reached RRs of only 0.6 – 0.8, relative to nonusers, with extended use. Despite its magnitude, there are several reasons to be skeptical about this result. The protective effect was most pronounced for general multivitamins and was attenuated when the actual content of the vitamin supplements was considered. Also, no analogous protective effect was noted for intake of the identical micronutrients in food. Finally, the reduction in risk associated with supplemental vitamin C or folate use was noted in women with relatively high, as well as relatively low, dietary intake of the respective micronutrient. It is quite likely that supplemental vitamin users adhered to other aspects of lifestyle, possibly involving sexual, contraceptive, or smoking practices, that were not perfectly measured in this study and that effectively reduced their risk of cervical cancer. This possibility is supported by the extensive confounding of the cervical cancer risks associated with supplemental vitamin use. However, it is also conceivable that only the women on supplemental vitamins attained high enough serum micronutrient levels for a sufficiently long period to affect carcinogenesis.

The other positive finding of this analysis was an apparent protective effect of dark yellow-orange vegetables on risk of *in situ* cervical cancer. Of the 15 dietary variables examined, only this one showed a significant trend in risk by quartiles of intake and a significantly elevated risk (RR = 1.9) at the lowest quartile of intake. The strong inverse association remained when deciles of intake were examined. However, the RR of 1.9 could be reduced to 1.6 by adjusting for multivitamin use. The inverse relationship between dark yellow-orange vegetables and risk of *in situ* cervical cancer was enhanced when analysis was restricted

to Denver subjects, and a comparable inverse relationship between dark yellow-orange vegetables and *invasive* cervical cancer was also noted in Denver, though not in all study centers combined.[1] It is difficult to decide whether limitation of this protective effect primarily to Denver subjects reflects a chance finding attributable to multiple comparisons or a valid observation resulting from the population representativeness of *in situ* and invasive case ascertainment in this particular study center. A reduction in risk of cervical cancer with intake of dark yellow-orange vegetables, but not dark green vegetables or total carotenoids, suggests a protective role for alpha-carotene. Preliminary high performance liquid chromatography determinations of the major carotenoids in common vegetables and fruits have indicated that although beta-carotene is found in both dark yellow-orange vegetables, such as carrots, and dark green vegetables, such as leafy greens, alpha-carotene is concentrated in dark yellow-orange vegetables.[35] In a recent case-control study of vulvar cancer, dark yellow-orange vegetables and alpha-carotene were the primary dietary determinants of reduced risk.[36] Although beta-carotene is the carotenoid generally discussed as an antioxidant, other carotenoids which share similar properties have not been adequately explored, and could partially explain the reduction in cancer risk associated with vegetable and fruit intake in epidemiologic studies.[37]

The absence of protective effects for carotenoids, vitamin A, vitamin C, and folate in our case-control study of invasive and *in situ* cervical cancer does not concur with the extensive published literature.[2-19,38,39] Even when only the five case-control studies that identified controls reasonably comparable to the cases and adjusted for most of the major cervical cancer risk factors in analysis are considered (Table 5), our results do not agree. All five studies—two hospital-based studies with hospital controls,[13,19] one hospital-based study with community

Table 5. Selected case-control studies of diet or nutrient status and cervical cancer

Authors, date	Study design	No. of cases, no. of controls (participation)	Extent of cervical disease	Exposures evaluated, methods	Evidence of association[a]
Harris *et al*, 1986	Cases from two hospitals and one health center in Oxford, England; hospital/clinic controls with benign gynecologic problems	32, 226 (<40 - 50%)[b]	Invasive	Serum usually collected during radiotherapy	
				Beta-carotene	—
				Vitamin A	—
		81, 226 (<40 - 50%)[b]	*In situ* (47%) + dysplasia (53%)	Serum collected prior to treatment	
				Beta-carotene	+,[tr],neg
				Vitamin A	—
Brock *et al*, 1988	Cases from two hospitals in Sydney, Australia; community controls matched on family physician	117, 196 (70%, 69%: interview)	*In situ*	Food frequencies and portion sizes for 160 items	
				Carotenoids	—[c]
				Vitamin A	—
				Vitamin C	(tr),neg
				Folate	—
		100, 143 (60%, 50%: blood draw)		Plasma collected after diagnosis	
				Total carotenoids	—[c]
				Beta-carotene	+,tr,neg
				Vitamin A	—
La Vecchia *et al*, 1988[d]	Cases from three hospital centers in Milan, Italy; hospital controls with acute conditions	392, 392 (98%, 98%)[e]	Invasive	Food frequencies for five items[f]	
				Green vegetables	+,tr,neg
				Carrots	+,tr,neg
				Milk	+,tr,neg
				Liver	—
	Cases from screening clinics of three hospital centers in Milan; clinic controls with normal cervical smears at screen	247, 247 (98%, 98%)[e]	*In situ*/severe dysplasia (55%) + moderate, mild dysplasia (44%)	Green vegetables	—
				Carrots	—
				Milk	—
				Liver	—

Table 5. *Continued.*

Authors, date	Study design	No. of cases, no. of controls (participation)	Extent of cervical disease	Exposures evaluated, methods	Evidence of association[a]
Verreault *et al*, 1989	Population-based case series from three Seattle, Washington counties; controls by random digit dialing	189, 227 (50%,[g] 69%)	Invasive	Food frequencies for 66 items	
				Carotenoids	(tr),neg
				Vitamin A	—
				Vitamin C	[+],tr,neg
				Folate	—
				Vitamin E	+ ,tr,neg
Slattery *et al*, 1990	Population-based case series from four urban Utah counties; population controls by random digit dialing	266, 408 (66%, 76%)	Invasive (87%) + *in situ* (13%)	Food frequencies and typical portion and preparation for 183 items	
				Carotenoids	—
				Vitamin A	—
				Vitamin C	(+),neg
				Vitamin E	(+),neg
				Selenium	(+),neg
Ziegler *et al*, 1990	Cases from 24 hospitals in five US areas; community controls, matched on telephone exchange, by random digit dialing	271, 502 (73%, 74%)	Invasive	Food frequencies for 75 items	
				Carotenoids	—
				Vitamin A	—
				Vitamin C	—
				Folate	—

[a]A + indicates a statistically significant association; *e.g.* a significant difference in diet or nutrient status between cases and controls or a significant difference in RRs for subgroups of the population stratified by diet or nutrient status; (+) indicates an apparent association that was not statistically significant; [+] indicates a marginally significant association. Tr indicates a statistically significant test for trend in RRs with changes in diet or nutrient status; (tr) indicates an apparent trend that was not statistically significant; [tr] indicates a marginally significant trend. Neg implies a decreased risk of cancer with increased dietary intake or nutrient levels. (—) indicates that no evidence for an association or trend was observed. Results are based on fully adjusted models.

[b]Exact participation rates could not be determined from relevant publications.[13,40]

[c]Model for each dietary (or plasma) nutrient included all other dietary (or plasma) nutrients.

[d]Includes the study subjects analyzed in La Vecchia *et al*, 1984.

[e]Separate participation rates for cases and controls for each phase of study were not presented.[19]

[f]Too few food items to form quantitative measures of nutrient intake.

[g]Thirty percent of the eligible cases died prior to the study, and surrogates were not interviewed.

controls,[18] and two population-based studies[38,39]—have found a reduction in risk of cervical cancer associated with the micronutrients that are concentrated in vegetables and fruits, specifically carotenoids, vitamin C, and folate, or with intake of vegetables and fruits themselves. Recently, two studies, both population-based, found these protective effects for invasive disease[38,39] although our hospital-based study with community controls did not.[1] On closer examination, there are several other disturbing inconsistencies in the literature on diet and cervical cancer. One study noted a protective effect for invasive, but not *in situ*, cervical cancer;[19] another study noted a protective effect for dysplasia and *in situ* disease, but not for invasive disease;[14] the other three studies in Table 5, excluding ours, focused on only one kind of cervical abnormality. The five studies that evalauted vitamin A[13,18,19,38,39] and the two studies that evaluated folate[18,38] reported no effect, as did our study. Carotenoids seemed protective in four[13,18,19,38] of the five studies, other than ours, that evaluated them; and vitamin C seemed protective in all three of three studies, other than ours, that evaluated them.[18,38,39] However, the micronutrient associated with the most striking reduction in risk, after adjustment for other cervical cancer risk factors, were not the same among the three studies that evaluated a series of micronutrients. The strongest effect was noted for beta-carotene in one study,[18] vitamin E in another study,[38] and selenium in a third.[39] Although the increase in risk associated with low carotenoids or vitamin C was generally sizeable (adjusted RRs for the lowest quartile or quintile, relative to the highest quartile or quintile, reached two[38] for dietary carotenoids;

three[13] and five[18] for blood beta-carotene; and two for dietary vitamin C,[38] adjusted RRs of 1.5 for dietary vitamin C[39] and less than 1.2 for dietary carotenoids[39] have also been observed and reported as indicative of protection.

It is not immediately obvious why the dietary results of our study of invasive and *in situ* cervical cancer do not agree with the published epidemiologic literature. We compared our median levels and interquartile ranges of intake for carotenoids, vitamin C, and folate with those of the three other case-control studies of cervical cancer that utilized comprehensive food frequency interviews[18,38,39] and found our study was remarkably similar to the others.

Two of the studies presented in Table 5, other than ours, asked about multivitamin use. Regular use of multivitamins was inversely related to risk of cervical cancer (RR = 0.5 - 0.7) in one study,[18] but unrelated in the other.[38] The same two studies also evaluated food group intake, but neither investigated dark yellow-orange vegetables specifically. One reported a strong inverse association (P for trend = 0.06) with dark green and yellow vegetable consumption;[38] the other found no protective effect for this food group.[18] Like our study, neither of the two studies found reductions in risk of cervical cancer associated with total vegetable or total fruit intake.[18,38] The protective effects we noted for multivitamins and dark yellow-orange vegetables are provocative, but need to be replicated.

In summary, the risk of *in situ* and invasive cervical cancer was not reduced by high dietary intake of carotenoids, vitamin A, vitamin C, or folate in our case-control study in white US women. Our negative findings for these micronutrients do not agree with much of the published literature. The reasons are not clear. Our results, along with other inconsistencies in the literature, introduce a note of caution into the dietary intervention studies planned for this cancer and suggest that the role of micronutrients in the etiology of cervical cancer is not yet resolved.

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References

1. Ziegler RG, Brinton LA, Hamman RF, *et al.* Diet and the risk of invasive cervical cancer among white women in the United States. *Am J Epidemiol* 1990; **132:** 432 - 45.
2. Hirayama T. Diet and cancer. *Nutr Cancer* 1979; **1:** 67 - 81.
3. Wassertheil-Smoller S, Romney SL, Wylie-Rosett J, *et al.* Dietary vitamin C and uterine cervical dysplasia. *Am J Epidemiol* 1981; **114:** 714 - 24.
4. Romney SL, Palan PR, Duttagupta C, *et al.* Retinoids and the prevention of cervical dysplasias. *Am J Obstet Gynecol* 1981; **141:** 890 - 4.
5. Lambert B, Brisson G, Bielmann P. Plasma vitamin A and precancerous lesions of cervix uteri: A preliminary report. *Gynecol Oncol* 1981; **11:** 136 - 9.
6. Butterworth CE Jr, Hatch KD, Gore H, Mueller H, Krumdieck, CL. Improvement in cervical dysplasia associated with folic acid therapy in users of oral contraceptives. *Am J Clin Nutr* 1982; **35:** 73 - 82.
7. Marshall JR, Graham S, Byers T, Swanson M, Brasure J. Diet and smoking in the epidemiology of cancer of the cervix. *JNCI* 1983; **70:** 847 - 51.
8. Bernstein A, Harris B. The relationship of dietary and serum vitmin A to the occurrence of cervical intraepithelial neoplasia in sexually active women. *Am J Obstet Gynecol* 1984; **148:** 309.
9. La Vecchia C, Franceschi S, Decarli A, *et al.* Dietary vitamin A and the risk of invasive cervical cancer. *Int J Cancer* 1984; **34:** 319 - 22.
10. Wylie-Rosett JA, Romney SL, Slagle NS, *et al.* Influence of vitamin A on cervical dysplasia and carcinoma *in situ*. *Nutr Cancer* 1984; **6:** 49 - 57.
11. Orr JW Jr, Wilson K, Bodiford C, *et al.* Nutritional status of patients with untreated cervical cancer II. Vitamin assessment. *Am J Obstet Gynecol* 1985; **151:** 632 - 5.
12. Romney DL, Duttagupta C, Basu J, *et al.* Plasma vitamin C and uterine cervical dysplasia. *Am J Obstet Gynecol* 1985; **151:** 976 - 80.
13. Harris RWC, Forman D, Doll R, Vessey MP, Wald NJ. Cancer of the cervix uteri and vitamin A. *Br J Cancer* 1986; **53:** 653 - 9.
14. Heinonen PK, Kuoppala T, Koskinen T, Punnonen R. Serum vitamins A and E and carotene in patients with gynecologic cancer. *Arch Gynecol Obstet* 1987; **241:** 151 - 6.
15. Romney SL, Basu J, Vermund S, Palan PR, Duttagupta C. Plasma reduced and total ascorbic acid in human uterine cervix dysplasia and cancer. *Annals NY Acad Sci* 1987; **498:** 132 - 43.
16. Janik P, Stelmachow J, Sawicki J, Swietochowska B, Kwasniewsky SW, Panek G. Serum retinol level in patients with pre and malignant lesions of female genital tract. *Eur J Gynaec Oncol* 1987; **8:** 595 - 7.
17. Palan PR, Romney SL, Mikhail M, Basu J. Decreased plasma beta-carotene levels in women with uterine cervical dysplasias and cancer. *JNCI* 1988; **80:** 454 - 5.
18. Brock KE, Berry G, Mock PA, MacLennan R, Truswell AS, Brinton LA. Nutrients in diet and plasma and risk of *in situ* cervical cancer. *JNCI* 1988; **80:** 580 - 5.
19. La Vecchia C, Decarli A, Fasoli M, *et al.* Dietary vitamin A and the risk of intraepithelial and invasive cervical neoplasia. *Gynecol Oncol* 1988; **30:** 187 - 95.
20. Jones CJ, Brinton LA, Hamman RF, *et al.* Risk factors for *in situ* cervical cancer: Results from a case-control study. *Cancer Res* 1990; **50:** 3657 - 62.
21. Waksberg J. Sampling methods of random digit dialing. *J Am Stat Assoc* 1978; **73:** 40 - 6.
22. Hartge P, Brinton LA, Rosenthal JF, Cahill JI, Hoover RN,

Waksberg J. Random digit dialing in selecting a population-based control group. *Am J Epidemiol* 1984; **120:** 825 – 33.
23. Brinton LA, Schairer C, Haenszel W, *et al.* Cigarette smoking and invasive cervical cancer. *JAMA* 1986; **255:** 3265 – 9.
24. National Center for Health Statistics. Plan and operation of the second National Health and Nutrition Examination Survey, 1976 – 1980, Vital and Health Statistics. Programs and Collection Procedures. Series 1 Number 15. Hyattsville, MD: US DHHS, 1981.
25. US Department of Agriculture. *Composition of Foods.* Agriculture Handbook No. 8. Washington, DC: US GPO, 1963.
26. National Academy of Sciences. *Recommended Dietary Allowances, 9th revised edn.* Washington, DC: NAS, 1980.
27. US Department of Agriculture. *Composition of Foods.* Agriculture Handbooks Nos. 8-1 to 8-16. Washington, DC: US GPO, 1976 – 1986.
28. Subar AF, Block G, James LD. Folate intake and food sources in the US population. *Am J Clin Nutr* 1989; **50:** 508 – 16.
29. Breslow NE, Day NE. *Statistical Methods in Cancer Research. Vol. 1. The Analysis of Case-Control Studies.* Lyon: International Agency for Research on Cancer, 1980; IARC Sci. Pub. No. 32.
30. US Department of Commerce. *1980 Census of Population.* Washington, DC: USGPO, 1982 – 1984.
31. Ziegler RG, Mason TJ, Stemhagen A, *et al.* Carotenoid intake, vegetables, and the risk of lung cancer among white men in New Jersey. *Am J Epidemiol* 1986; **123:** 1080 – 93.
32. Whitehead N, Reyner F, Lindenbaum J. Megaloblastic changes in the cervical epithelium: Association with oral contraceptive therapy and reversal with folic acid. *JAMA* 1973; **226:** 1421 – 4.
33. Brinton LA, Huggins GR, Lehman HF, *et al.* Long-term use of oral contraceptives and risk of invasive cervical cancer. *Int J Cancer* 1986; **38:** 339 – 44.
34. Koutsky LA, Galloway DA, Holmes KK. Epidemiology of genital human papilomavirus infection. *Epidemiol Revs* 1988; **10:** 122 – 63.
35. Micozzi MS, Beecher GR, Taylor PR, Khachik F. Carotenoid analyses of selected raw and cooked foods associated with a lower risk for cancer. *JNCI* 1990; **82:** 282 – 5.
36. Sturgeon S, Ziegler RG, Brinton LA, Nasca P, Mallin K. Diet and the risk of vulvar cancer. *Ann Epidemiol* 1991; in press.
37 Ziegler RG. Vegetables, fruits, and carotenoids and the risk of cancer. *Am J Clin Nutr* 1991; in press.
38. Verrault R, Chu J, Mandelson M, Shy K. A case-control study of diet and invasive cervical cancer. *Int J Cancer* 1989; **43:** 1050 – 4.
39. Slattery ML, Abbott TM, Overall JC Jr, *et al.* Dietary vitamins A, C, and E and selenium as risk factors for cervical cancer. *Epidemiology* 1990; **1:** 8 – 15.
40. Harris RWC, Brinton LA, Cowdell RH, *et al.* Characteristics of women with dysplasia or carcinoma *in situ* of the cervix uteri. *Br J Cancer* 1980; **42:** 359 – 69.